UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/979,518	04/10/2002	Judith E Meis	310307.90134	6310

7590 09/28/2009

Jean C Baker
Quarler & Brady
411 East Wisconsin Avenue
Milwaukee, WI 53202-4497

EXAMINER	
HUTSON, RICHARD G	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
09/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/979,518	MEIS, JUDITH E	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60,61,63,64,66 and 67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60,61,63,64,66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/22/2009; 6/25/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/27/2009 has been entered.

Claims 60, 61, 63, 64, 66 and 67 are present and at issue for examination.

Applicants' arguments filed on 7/27/2009, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 60, 61, 63, 64, 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roche Molecular Biochemicals Catalog, 1999, pages 50-51,)See

IDS), Sellman et al. (Journal of Bacteriology, Vol 174, No. 13, pages 4350-4355, see IDS, July 1992) and Lu et al., (BioFeedback, Vol 11, No. 4, pages 464-466, 1991, See IDS).

This rejection was stated in the previous office action as it applied to previous claims 60, 61, 63, 64, 66 and 67. In response to this rejection, applicants have not amended the claims, but rather traverse the rejection as it applies to the claims.

As previously stated, Roche Molecular Biochemicals Catalog, 1999 teaches a one step RT-PCR System and methodologies comprising incubating RNA templates in a buffer solution containing dNTPs and one or more primers complementary to at least a portion of one or more of the RNA templates with a purified DNA polymerase from *Carboxydothermus hydrogenoformans* and a *Taq* DNA polymerase, in the presence of 12.5 mM Mg and in the substantial absence of Manganese. Roche Molecular Biochemicals Catalog, 1999 further teach that while other thermoactive DNA polymerase with reverse transcriptase activity use manganese ions as co-factors, manganese has a negative effect on the fidelity of DNA synthesis.

Sellman et al. teach the purification and characterization of DNA polymerase from various species of *Bacillus*. Spellman et al. specifically teach the DNA polymerase enzymes from *Bacillus Stearothermophilus* require Mg^{2+} for optimal activity (See abstract). Sellman et al. also teach that the Bst DNA polymerase had its greatest activity at a concentration of magnesium of 10mM and that the addition of more magnesium did not result in a significant increase in polymerase activity.

Lu et al. teach that subtilisin digestion of the Bst polymerase I holoenzyme results in a large fragment that results in the same uniform DNA synthesis as the orginal full-length enzyme and that this fragment is stable at ambient temperature.

One of skill in the art at the time of the invention would have been motivated to practice methods similar to those taught by the Roche Molecular Biochemicals Catalog, 1999, with the exception of replacing the purified DNA polymerase from *Carboxydothermus hydrogenoformans* and *Taq* DNA polymerase with the DNA polymerase from Bacillus stearothermophilus as taught by either Sellman et al. or Lu et al. in order to convert a RNA template to a cDNA template and amplify the synthesized cDNA via a polymerase chain reaction. The expectation of success is high based upon the similar methods taught by Sellman et al. and those taught by Lu et al. who teach similar DNA synthetic reactions using Bst DNA polymerase. Further given the results of Sellman et al. and Lu et al. and Roche Molecular Biochemicals Catalog, 1999, the substitution of the Bst DNA polymerases taught by Sellman et al. or Lu et al. into the methods taught by Roche Molecular Biochemicals Catalog, 1999 would yield predictable results.

Thus claims 60, 61, 63, 64, 66 and 67 are obvious over Roche Molecular Biochemicals Catalog, 1999, Sellman et al. and Lu et al.

Applicants continue to traverse this rejection on much of the same basis that applicants have previously traversed.

First, applicants submit that it was and still is widely known that most DNA polymerases do not have reverse transcriptase activity in the presence of Mg2+ and in

the absence of Mn2+ and thus, the fact that Spellman and/or Lu teach that Bst DNA polymerase requires Mg2+ for optimal DNA-dependent DNA polymerase activity is irrelevant to whether or not a particular DNA polymerase has reverse transcriptase activity or to whether or not such reverse transcriptase activity, if it exists at all, requires Mn2+.

Second, applicants submit that specific and widely known information in the art concerning the reverse transcriptase activity of Bst DNA polymerase taught that Mn2+ ions were required for such reverse transcriptase activity and that in contrast, the present claims recite methods for preparing Bst DNA polymerase holoenzyme or a Bst DNA polymerase large fragment for reverse transcription of RNA molecules in the presence of Mg2+ ions and in the absence of Mn2+ ions. Applicants submit that even though Bst DNA polymerase is widely known to one of skill in the art, references in the art at the time of the present invention specifically teach that Bst DNA polymerase had reverse transcriptase activity only in the presence of Mn2+ ions.

Applicants submit that to the best of Applicants knowledge, in spite of the long period during which one of the forms (i.e., a holoenzyme or a large fragment) of Bst DNA polymerase has been used, the first experimental demonstration that Bst DNA polymerase has reverse transcriptase activity appears to have been in U.S. Patent No. 6,030,814 to Jerome J. Jendrisak ("Jendrisak") which issued on February 29, 2000. (Applicants note that Jerome J. Jendrisak is Vice President of Research and Development at Epicentre Technologies, of Madison, Wisconsin, the assignee of the present application).

Applicants submit that Jendrisak clearly teaches that Bst DNA polymerase, like Tth DNA polymerase, is a manganese-dependent reverse transcriptase. For example, in the Abstract Jendrisak states:

"A method of improving the synthesis of full-length cDNA transcripts by Mn++ -dependent reverse transcriptases, preferably DNA-dependent DNA polymerases, is disclosed." *(emphasis added).*

Applicants submit that Jendrisak goes on to show that addition of betaine to the reaction mixture improves the reverse transcriptase activity of Tth DNA polymerase and Bst DNA polymerase when manganese is included in the reaction mixture. For example, in the fifth paragraph of the Detailed Description of the Invention, Jendrisak states:

"The examples below describe a typical reverse transcription reaction mixture. A preferred reaction mixture includes RNA template molecules, oligonucleotide primers, a mixture of all four dNTPs, and a suitable buffer. The examples below disclose the use of a buffer comprising 0.01 M Tris-HC1, pH 8.3, 0.05 M KC1, 1.5 mM MgC12 and 0.75 mM MnC~. U.S. Pat. Nos. 5,322,770; 5,310,652; and 5,407,800 describe Mn-dependent reverse transcription reactions." *(emphasis added).*

Finally applicants submit that neither Roche, nor Sellman or Lu, either alone or in combination, teach or suggest the subject matter of the pending claims. The pending claims recite the DNA polymerase from *Bacillus stearothermophilus (Bst)* type strain 5 having reverse transcriptase activity in the absence of manganese ions. Nothing in

Roche, Sellman or Lu teach or suggest that replacing the enzyme of Roche with the *Bacillus stearothermophilus (Bst)* type strain 5 polymerase of the pending claims, a polymerase known at the time of Applicants invention to have reverse transcriptase activity only in the presence of manganese ions, will be feasible, let alone successful. Accordingly, Applicants respectfully submit that the pending claims are not obvious over Roche in view of Sellman and/or Lu. Withdrawal is requested.

Applicant's complete argument is acknowledged and has been carefully considered, however, is not found persuasive for the reasons previously made of record and repeated herein.

As previously stated, one of skill in the art at the time of the invention would have been motivated to practice methods similar to those taught by the Roche Molecular Biochemicals Catalog, 1999, of a one step RT-PCR System and methodologies comprising incubating RNA templates in a buffer solution containing dNTPs and one or more primers complementary to at least a portion of one or more of the RNA templates with a purified DNA polymerase, in the presence of 12.5 mM Mg and in the substantial absence of Manganese, with the exception of replacing the purified DNA polymerase from *Carboxydothermus hydrogenoformans* and *Taq* DNA polymerase with the DNA polymerase from Bacillus stearothermophilus, as taught by either Sellman et al. or Lu et al. in order to convert a RNA template to a cDNA template and amplify the synthesized cDNA via a polymerase chain reaction. The basis of such a method absent manganese is that Roche teach that manganese has a negative effect on the fidelity of DNA synthesis. The expectation of success is high based upon the similar methods taught

by Sellman et al. and those taught by Lu et al. who teach similar DNA synthetic reactions using Bst DNA polymerase. Further given the results of Sellman et al. and Lu et al. and Roche Molecular Biochemicals Catalog, 1999, the substitution of the Bst DNA polymerases taught by Sellman et al. or Lu et al. into the methods taught by Roche Molecular Biochemicals Catalog, 1999 would yield predictable results.

With regard to applicants submission that it was and still is widely known that most DNA polymerases do not have reverse transcriptase activity in the presence of Mg2+ and in the absence of Mn2+, applicants have not provided evidence to support applicants preferred conclusion and the teaching of Roche Molecular Biochemicals Catalog of such reverse transcriptase reaction conditions in the absence of manganese, is in contrast to such.

With regard to applicants submission that references in the art at the time of the present invention specifically teach that Bst DNA polymerase had reverse transcriptase activity only in the presence of Mn2+ ions and applicants submission of U.S. Patent No. 6,030,814 to Jerome J. Jendrisak ("Jendrisak") which issued on February 29, 2000 to support this position are not found persuasive on the basis that applicants evidence does not support that Bst DNA polymerase had reverse transcriptase activity only in the presence of Mn2+ ions. Certainly applicants submission supports that Bst DNA polymerase had reverse transcriptase activity in the presence of Mn2+ ions, but not only in the presence of Mn2+ ions.

Thus the combination of the teachings of Roche Molecular Biochemicals Catalog, 1999, Sellman et al. and Lu et al. provides the motivation to practice similar methods with similar reaction conditions for the two magnesium dependent DNA polymerases, especially with regard to the presence of magnesium and the absence of manganese.

Thus, claims 60, 61, 63, 64, 66 and 67 remain obvious over Roche Molecular Biochemicals Catalog, 1999, Sellman et al. and Lu et al.

Art of Record

Karkas, Reverse Transcription by *Echerchia coli* DNA Polymerae I, PNAS, Vol. 70, No.art I, pp 3834-3838, December 1973.

Conclusion

This is a continuation of applicant's earlier Application No. 09/979,518. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh

9/25/2009

/Richard G Hutson/
Primary Examiner, Art Unit 1652